Maternal morbidity and mortality in the Netherlands and their association with obstetric interventions

Kallianidis, A.F.

General Introduction

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INTRODUCTION

A 30-year-old woman, Mrs H, with a previous caesarean section, this time around hoped for an uncomplicated pregnancy. She was healthy and pregnant with a singleton. At the screening ultrasound at 20 weeks' gestation, complete placenta previa was diagnosed. Ultrasonographic follow-up at 32 weeks did not reveal signs of invasive placentation with the placenta in a low anterior position. Therefore, at early term, a planned repeat caesarean section was performed. The obstetricians were confronted with an undiagnosed abnormally invasive placenta, invading into the uterine serosa. After extracting the foetus from a uterine incision higher up in the uterus, massive haemorrhage occurred following efforts to remove the placenta. Oxytocin, sulprostone, tranexamic acid, calcium gluconate and surgical ligation of the internal iliac arteries were unsuccessful in stopping the bleeding. There was no time left for additional uterus-sparing interventions, such as radiological uterine artery embolization. In an ultimate attempt to control the haemorrhage, emergency peripartum hysterectomy was performed, with the woman in severe hypovolaemic shock. Post-operatively she was admitted in the intensive care unit (ICU) for haemodynamic support and treatment of the coagulopathy secondary to the massive blood loss. Perioperative severe hypovolaemia resulted in irreversible cerebral damage and the woman died a few days later, without ever having seen her newborn baby, leaving behind her partner, family and friends. (Reported case of maternal mortality from the Dutch Audit Committee Maternal Mortality and Morbidity - Anonymised and modified in order not to be identifiable)

Death during childbirth is a devastating event. Many questions will arise among those confronted with this tragedy. Was the death of this woman preventable? Would the outcome have been different had the invasive placenta been diagnosed on forehand? What would have been the optimal management of the acute, massive obstetric haemorrhage? Would management have been different in another hospital or country? To what extent is this death attributable to the previous caesarean section? Which lessons can be learned in order to prevent similar calamities from happening to other women?

The importance of maternal deaths in the history of mankind is signified by Greek mythology describing maternal death and birth by what we nowadays know to be caesarean section. Striking is the mythological description of Asclepius' birth, the God of medicine and healing, which was by 'peri-' or 'post-mortem' caesarean section. Asclepius was the son of Apollo, the god of the sun, and Coronis, a mortal woman. During her pregnancy, Coronis fell in love with Ischys, a mortal man. Once Apollo learned of her infidelity, he killed Coronis, with the help of his sister Artemis. Out of remorse, when the dead body of the pregnant Coronis lay on the funeral fire, Apollo extracted Asclepius from the womb (Figure 1).

Figure 1. Woodprint from 1549 edition of Alessandro Benedetti's De Re Medica. The Birth of Asclepius. (Source: Cesarian Section - birth of Aesculapius - Benedetti, A. De re medica, Venice, 1533, Digital Collection of U.S. National Library of Medicine http://resource.nlm.nih.gov/101450734)

PART 1 - MATERNAL MORTALITY - IN THE NETHERLANDS

During the course of uncomplicated pregnancies, women and their families look forward to what usually results in a joyful life event, childbirth. For the vast majority, the course of pregnancy will indeed be uneventful and uncomplicated. However, for a small number of women this will not be the case as unforeseen complications can always occur. Even in healthy women, pregnancy and childbirth can lead to complications, ranging from minor, self-limiting conditions mainly causing discomfort to life-threatening conditions with life-long sequalae or even death. Such complications can arise from obstetric conditions but may also be the result of the physiological adaptation of the female body to the pregnancy, during which previously 'hidden' underlying and undiagnosed conditions can come to light, or arise from the deterioration of mild, pre-existing conditions.

According to the World Health Organization (WHO) maternal mortality is defined as 'the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes'.[1] It is an important indicator of the quality of obstetric care and, in essence, can be seen as the uttermost form of maternal morbidity. (Figure 2) Reduction of maternal mortality by 75% by the year 2015, was

one of the eight Millennium Development Goals proposed in 2000. Notwithstanding some astonishing progress, this target remained far from achieved, with the global reduction stabilising at 45% from the 1990-level.[2] This was followed up by the Sustainable Development Goals in 2015, in which further reduction of maternal mortality to less than 70 per 100,000 live births was again prioritised.

Most women die in low-income countries, which carry the largest burden of maternal morbidity and mortality. But also in several middle- and high-income countries, maternal health is under pressure. This pressure has been compounded by the recent COVID-19 pandemic, which indirectly affected maternal health tremendously, with resources being diverted away from maternity services and restricted access to emergency care. As a result, considerable increases in maternal and perinatal mortality and severe morbidity have been witnessed, due to disruption of routine health care and increases of patient and facility delays, in health systems that were often already failing at the onset of the pandemic.[3]

The frequency of maternal deaths in populations is expressed as the maternal mortality ratio (MMR): the number of maternal deaths per 100,000 livebirths. Traditionally, causes of maternal mortality are divided into direct and indirect causes. The former result directly from obstetric disease or pregnancy complications and the latter from non-obstetric - usually pre-existing- disease, aggravated by the physiological effects of pregnancy. Non-pregnancy related 'fortuitous' deaths due to traffic accidents or violence are excluded from calculations of the MMR.

The dichotomous classification into direct and indirect, however, has started to lose its meaning in recent times.[4] During past decades, non-obstetric conditions have become more prevalent, at least in the more privileged parts of the world, leading to increasing incidence of indirect as well as direct complications. For instance, morbidly obese women are at higher risk of cardiological 'indirect' complications (such as arrythmia) as well as 'direct' obstetric complications such as pregnancy-related thrombo-embolism or postpartum haemorrhage. In this way, an increase of the MMR related to direct causes of death may not necessarily reflect poor management of obstetric haemorrhage but could also represent changing risk profiles. Moreover, classification of death by suicide during pregnancy and the postpartum period also changed following the introduction of the new ICD-MM classification of maternal deaths.[5] Previously, suicide was generally classified as 'indirect', with pregnancy seen to aggravate pre-existing psychiatric conditions, or even as 'fortuitous' when no pre-existing psychiatric conditions were present. This categorization is often difficult and arbitrary, and in order to highlight maternal deaths due to suicide as one clear entity, these are nowadays uniformly classified as a direct deaths.[6]

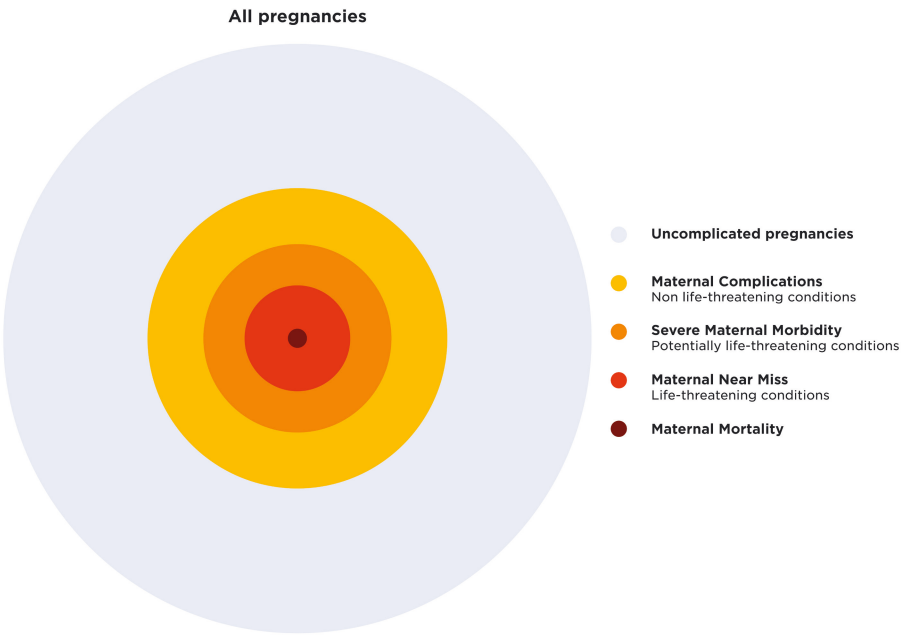

Figure 2. The circle of disease. From uncomplicated pregnancy to maternal mortality. Adapted from the Pyramid of Disease.

Maternal mortality has been registered in The Netherlands since 1950 by Statistics Netherlands (*Centraal Bureau voor de Statistiek*), where all vital statistics of the country are registered. However, use of vital statistics only, based on information from death certificates is known to give substantial underestimation of maternal deaths.[7] In 1981, the Maternal Mortality Committee (MMC) was installed, a committee of the Netherlands Society of Obstetrics and Gynaecology (*Nederlandse Vereniging van Obstetrie en Gyaecologie*). Aim of the committee is systematic registration and classification of maternal deaths, and -by means of confidential enquiry- identification of lessons learned from each death. Confidential enquiry is a multi-disciplinary anonymous investigation of all maternal deaths, by means of which numbers and causes of deaths, as well as improvable factors in care are identified.[8] Being relatively labour-intensive, it can only be performed for small numbers of maternal deaths at a time, and is usually done on a nationwide scale in high-income countries as well as some middle-income countries such as South Africa and Namibia. Basis of the enquiry forms full accessibility to medical reports, maternity registers, theatre charts and laboratory results, as well as anonymity of women and health workers to overcome barriers to reporting. Improvable factors, previously called 'substandard care factors', are identified after examining the care given during pregnancy and childbirth and the events leading to death. Improvable factors can be identified in any aspect of care which might have had a negative

effect, even if it had no major impact on the final outcome. Standards of care are informed by national guidelines and, in their absence, best available evidence. Explicitly, the purpose of confidential enquiries is to operate outside the medico-legal realm. Rather, its aim is educational: to draw lessons from each woman's death, and feed these lessons back to professionals to avoid future deaths. After incorporation of the Netherlands Obstetric Surveillance System (NethOSS) into the MMC in 2016, the committee became the Dutch Audit Committee Maternal Mortality and Morbidity (*Auditcommissie Maternale Sterfte en Morbiditeit, AMSM*). Since 2019, the AMSM has been comprised of eight senior consultants in obstetrics and gynaecology, one obstetric anaesthesiologist, one midwife and two registrars in obstetrics and gynaecology.

In The Netherlands, registration of maternal mortality relies on reporting of deaths during pregnancy, and up to one year after birth or termination of pregnancy to the AMSM. Reporting is described as mandatory in the national guideline on maternal mortality. Any failure to do so is considered substandard.[9] Midwives, obstetricians, general practitioners and any other medical specialists may report the death of a woman. Until 2011, unreported maternal deaths were identified after annual cross-checking with Statistics Netherlands. Data reported to Statistics Netherlands about maternal deaths, however, rely on vital information recorded on death certificates, which is neither exhaustive in identifying all maternal deaths up to one year postpartum, nor specific enough to identify the cause of death in a majority of cases. Relying on routine vital statistics as reported to Statistics Netherlands resulted in an estimated level of underreporting of maternal deaths of around 26-33%. Crosslinking death and birth registries resulted in an estimated level of underreporting to the AMSM of 11%.[10] After 2011, no more cross-check took place as Statistics Netherlands considered that anonymity of reported cases could not be guaranteed, due to small numbers, with information potentially traceable to individual women.

An overview of the MMR in The Netherlands for the years 2000-2016, by use of data from Statistics Netherlands only -as reported to the WHO, is presented in Figure 3. Causes and frequency of maternal mortality in the Netherlands have been assessed twice before by means of confidential enquiry into maternal deaths. Schuitemaker et.al., for the years 1983 – 1992, identified 192 maternal deaths, leading to an MMR of 9.7 per 100,000 live births.[11] Leading cause of death was (pre-)eclampsia (n=51, 27%) followed by thromboembolism (n=21, 11%) and cerebrovascular conditions (n=19, 10%). The authors underlined the importance of being aware of risk factors for maternal mortality such as maternal age, parity and migrant status. In this study, medical records for one in five of the reported deaths were unavailable for confidential enquiry, which was significantly higher than reported in other countries with comparable enquiry systems such as the UK. In addition, the authors called for increasing the autopsy rate in maternal deaths, which stood at only 57% at the time. The most recent report on maternal mortality

in the Netherlands, before the report presented in this thesis, is that by Schutte et.al., which included the years 1993-2005.(10) With a total of 309 deaths, the MMR increased from 9.7 to 12.1 per 100,000 live births. Commonest cause of death remained (pre-)eclampsia (n=93, 30%) followed by cardiovascular disorders (n=45, 15%) and thromboembolism (n=44, 14%). This rise in MMR was attributed to better reporting of cases and demographic changes such as increases in the average age of pregnant women, and the proportions of non-native women and pregnant women with underlying conditions.

Around the same time, the 2010 *EuroPeristat* report on health and care of pregnant women and babies, listed the Netherlands below average in terms of perinatal mortality compared to other European countries.[12] This led to action across the country to improve the quality of maternal and perinatal health. Audit of perinatal death was implemented nationwide, led by Perinatal Audit Netherlands, later combined with the Perinatal Birth Registry into Perined.[13] The relatively high perinatal mortality rate in the Netherlands generated considerable media attention and led to important changes in the organization of the maternity care system and clinical practice, such as improvements in the collaboration between primary midwifery practices and secondary obstetric care. How come that these results regarding perinatal mortality led to such important policy changes, whilst the increasing maternal mortality ratio, reported around the same time, drew much less public attention?

The Netherlands has a relatively low MMR compared to other European countries, which all have ratios much below those of middle- and low-income countries.[14] Dutch maternal mortality ratios are usually compared to other European high-income countries like the UK, which has a longstanding history of a renowned system of confidential enquiry. Using relatively high numbers of maternal deaths and livebirths (approximately 200 maternal deaths and 2.2 million livebirths every 3 years), the MBRRACE-UK programme (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiry across the UK) of the national perinatal epidemiology unit in Oxford (NPEU) publishes robust annual reports on mortality rates and tri-annual reports on causes of death and trends in maternal mortality, as well as an in-depth analysis of risk factors. In the UK, the MMR has remained stable throughout recent years (2009-2017), around 9-10 per 100,000 livebirths.

For the years 2015-2017, the commonest causes of death in the UK were cardiac disease (23%), thromboembolism (16%) and cerebrovascular conditions (13%) while pre-eclampsia accounted for only 2%. This presents a striking difference with the Netherlands, where direct causes of death, foremost pre-eclampsia, have always been most frequent. There is worry that identification of indirect causes of deaths in the Netherlands might not be exhaustive. A particular question arising is: do we miss (late) maternal deaths, in particular of women who are managed by other medical specialists and who are not yet or not anymore under obstetric care, so particularly during early pregnancy or in the (late) postpartum period? Differences

in categorisation of causes of death could also explain some of the observed differences. For example, a woman with pre-eclampsia followed by severe obstetric haemorrhage during birth is classified as death due to haemorrhage in the UK but due to pre-eclampsia in the Netherlands.[15] However, even the combined proportion of pre-eclampsia and haemorrhage deaths in the UK does not even reach half the proportion of 35% of deaths due to (pre-)eclampsia in the Netherlands.

Maternal mortality trends in France, another high-income European country with an enhanced maternal mortality surveillance system, also differ from the Netherlands. While, for the years 1998 – 2007, direct causes of death also outnumbered indirect causes (66.2% vs 30.8%), haemorrhage has always been the leading cause (16%), followed by amniotic fluid embolism and thromboembolism (both 12%).[16] A comparison between the Netherlands and Italy reveals similar differences. In the Italian report on maternal mortality, conducted after crosslinking hospital discharge databases and death registries, commonest cause of death was 'non-pregnancy related causes', which included malignancies (39%) followed by violent deaths (17%) which both mostly occurred beyond the traditional 42-day postpartum interval. Regarding pregnancy-related causes, the most prevalent were haemorrhage, hypertensive disorders of pregnancy and cardiac disease, which are generally classified as 'indirect' pregnancy-related deaths.[17]

According to the concept of 'obstetric transition', as proposed by Souza et.al., during the process of maternal mortality reduction, countries progress through five stages. Starting with high maternal mortality ratios (MMR>1000), mostly due to direct obstetric causes, high fertility rates and high numbers of communicable diseases, progress occurs with improvement of infrastructure, equity in access to healthcare and eventually implementation of prevention strategies and better maternal and neonatal health care. In the latest stage of the obstetric transition (MMR <50 maternal deaths per 100 000 live births), indirect causes of maternal mortality and noncommunicable diseases become more prominent than direct causes.[18] In light of this obstetric transition, the question arises how the Netherlands, with an MMR around 10 per 100,000 live births, still finds its proportion of direct mortality exceeding that of indirect mortality.[10, 19]

While globally the ratios of maternal mortality show a steady decline, recent results from the United States, one of eight countries with a considerable rise in maternal mortality, come as a true wake-up call.[20] Figure 3, presents maternal mortality estimates for 2017 as well as trends since 2000, collected by the WHO and is based on vital statistics. Here the increase in te US can be clearly visualised. In a report from 2016, the MMR increased by 23% from 18.8 in 2000 to 23.8 per 100,000 live births in 2014. Reasons for this increase are still under debate. Much attention was directed to the newly added pregnancy checkbox to the standard death certificate, which was introduced in 2013, aiming for better ascertainment of maternal deaths. However, it was demonstrated that this improvement had only a limited effect on improved registration of maternal deaths and even led

to considerable ratios of false positives. Strikingly, racial-ethnic disparities remain extreme, with black women having a three times higher mortality risk compared to white women. This once more underlines the importance of regular quality assessment of maternal health outcomes and maternity care, also in high-income countries.

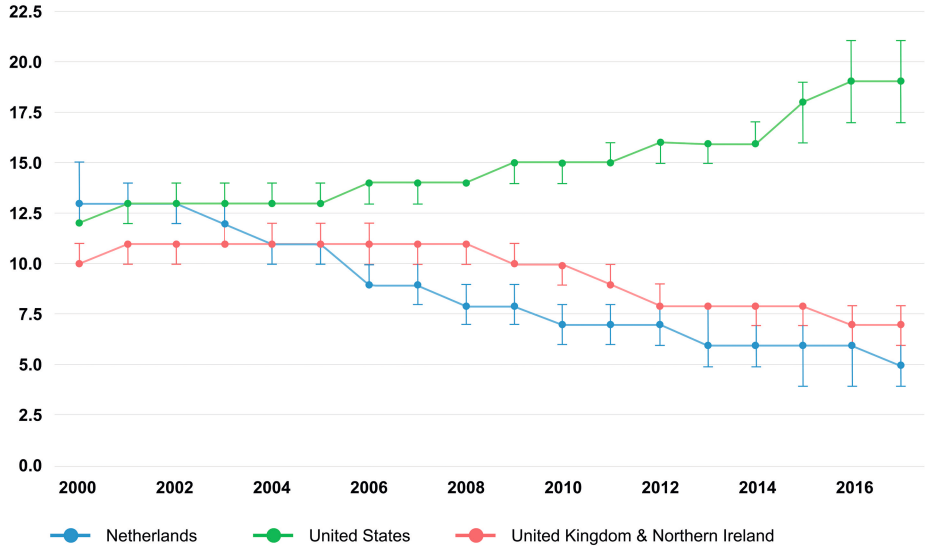

Figure 3. Maternal mortality ratios in the UK, US and the Netherlands, 2000 – 2017. (Source: MMR2017.srhr.org, WHO)

A decrease in mortality does not come by itself. Overtime, the prevalence of risk factors at the population level may change and so does medical practice, based on forthcoming evidence and insight. Most high- and upper middle-income countries progress or have progressed through the later stages of obstetric transition achieving lower MMRs with a concomitant higher prevalence of indirect causes of mortality. More women give birth in obstetric facilities and have access to obstetric interventions like caesarean section, induction and augmentation of labour. Availability and accessibility of medical interventions to assist during labour in case of complications are important, but optimal use might become overuse, referred to as "Too much too soon".[21] Every intervention comes with possible complications and therefore close monitoring of the association between interventions and adverse maternal outcome should not be neglected. [20]

Caesarean section is one of the interventions of which use has seen an unprecedented rise between 2000 and 2015, with the global rate having almost doubled from 12.1% to 21.1%.[22] Until the late 19th century, it was performed only after maternal death to extract the foetus, like Asclepius from the dead body of Ischys

and only in very rare cases were mothers reported so survive. In presence of modern anaesthesia, fine-tuned surgical procedures and post-operative care, caesarean section is considered a generally relatively safe procedure in high-income settings, for which the indications have become broader. When performed on evidence-based indications, it can be a lifesaving procedure for woman and foetus. However, rates of caesarean sections performed for non-medical indications, even at maternal request only, increase dramatically and this increase has downsides for maternal and perinatal health.[23]

A caesarean section rate of 9%-16% on a nationwide scale is considered optimal by the WHO and there appears to be no benefit above this rate on maternal and perinatal outcome.[24, 25] Availability and accessibility of caesarean section are considered necessary.[26] In some low-income countries, rates are still very low at the population level, leading to preventable maternal and foetal morbidity and mortality from impaired access to caesarean section. On the other hand, *at the facility level* in other low-, and middle-income countries and in many middle- and high-income countries even *at the population level*, overuse has become part of the caesarean pandemic.[22] For example, rates below 5% are observed in a few African countries while rates far exceeding 50% or even much higher are not uncommon in private healthcare facilities in China, Brazil and South Africa.[22, 27] In the Netherlands, caesarean section rates are relatively low compared to the rest of Europe, but have not escaped from the global increase, rising from 10% in 2000 to 14.9% in 2018.[28] (Figure 4)

Mode of birth and maternal outcome are closely linked. Caesarean section can be the result of unsuccessful vaginal birth or worsening pregnancy related or non-pregnancy related morbidity such as hypertensive disorders or cardiac disease leaving no window of opportunity for vaginal birth. At the same time, these women more often experience complications of the surgical procedure, ultimately even leading to maternal mortality, which can be regarded as the most extreme form of morbidity. (Figure 2) As such, the association of maternal death with caesarean section is even more pressing in light of the ever rising global caesarean section rates.[22] From an epidemiological perspective, it is challenging to measure the extent to which caesarean section contributes to a woman's death. Firstly, the initial events leading to death could have been present before surgery. Secondly, caesarean section might have been unavoidable, or even the best choice for the woman to give birth at that moment. And, last but not least, surgery itself can be the direct cause of death, or even totally unrelated to death. As such, confounding by indication hampers studies of causality or association in the retrospective design. In attempts to perform comparisons between vaginal birth and caesarean section, previous studies excluded women with pre-existing morbidity or even twin pregnancies.[29] Although this might facilitate comparisons, even in women with pre-existing morbidities and other risk factors the indication may be more or less evidence-based, and substantial variations exist between countries for these indications.

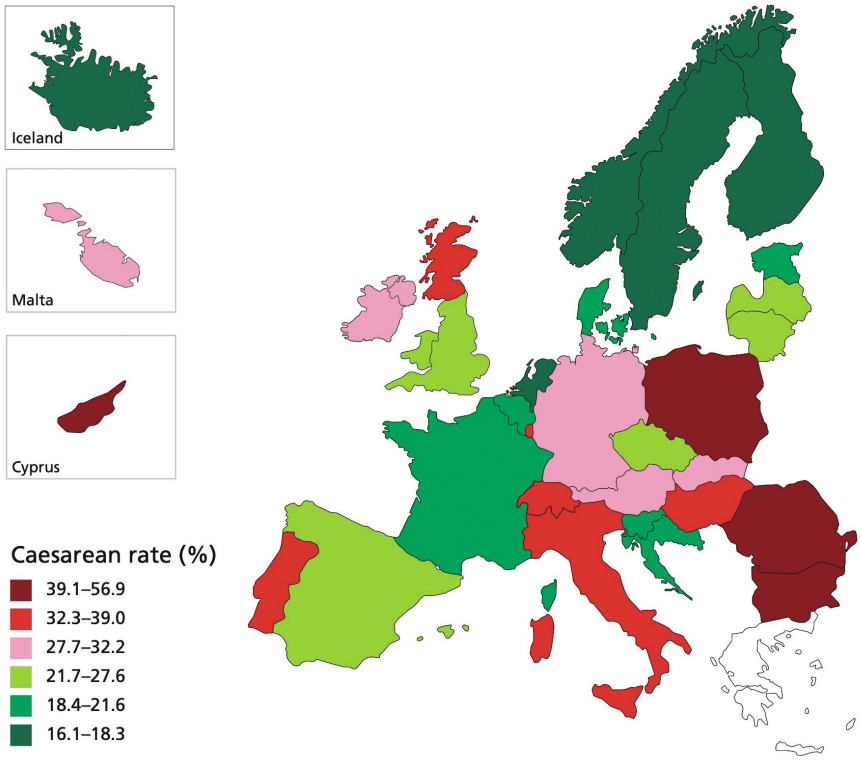

Figure 4. Caesarean section percentages in European countries. Figure form the European Perinatal Health report 2015 12

PART 2 - MATERNAL MORBIDITY

Maternal complications are unintended outcomes of pregnancy and childbirth resulting in negative short- or long-term outcomes for women. While maternal mortality can be seen as only the inner circle of maternal complications, a significant burden of disease is sustained by women with (potentially) life-threatening diseases. (Figure 2) Therefore, maternal morbidity has been added as a condition for audit in order to improve maternal health. Though the concept of maternal morbidity is not a new one, a discussion which definition best captures morbidity has been ongoing for a long time.[30, 31] In 2009, the WHO suggested the *maternal near miss* (MNM) approach to identify women with life-threatening conditions who survived: "a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy".[32]

Identification of women with 'potentially life threatening conditions' may use one of the following approaches:

1) clinical criteria (e.g. eclampsia);

2) intervention or treatment criteria (e.g. mass transfusion, admission to ICU, hysterectomy);

3) organ system disfunction criteria.

MNM is based on the concept of organ dysfunction and a core set of 25 "life-threatening conditions" is currently used.[32, 33]

As a result of improved maternity care, global ratios of maternal mortality had been declining up to the COVID-pandemic.[34] In a country like the Netherlands, usually between 10-20 maternal deaths are reported each year to the AMSM, including non-pregnancy related deaths as well as (extremely) rare pregnancy complications. Lessons can be drawn from each woman's death and maternal mortality will remain an undisputable quality indicator of healthcare. Given the small numbers of maternal deaths, it takes, however, decades before trends are detectable, and feedback aiming for improvement might be outdated already at the time more substantial numbers are collected. Therefore, focus has been shifted to maternal near misses, enabling more rapid collection of larger numbers, identification of risk factors at the population level and comparisons of maternal outcome between countries.

Combining maternal mortality and MNM forms the concept of severe maternal outcome (SMO). This concept stems from the common pathophysiology underlying all life threatening conditions: while some women will survive thanks to adequate and timely use of knowledge and care, others will die, sometimes only due to bad luck. The study of severe maternal outcome from obstetric complications such as severe postpartum haemorrhage or severe hypertensive disease of pregnancy is the cornerstone in improving management and thus maternal outcome. Rare pregnancy-related conditions, such as amniotic fluid embolism or acute fatty liver of pregnancy, are associated with high rates of mortality and morbidity. To acquire better data about such rare diseases and to arrive at clues for improved management, larger nationwide and internationally pooled studies are required.

In the Netherlands, the first nationwide registration of severe acute maternal morbidity and mortality (SAMM) was conducted in the years 2004-2006. Conceptually, SAMM differs from MNM, since SAMM can be seen to include also *potentially* life-threatening events. The LEMMoN study (*Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland)* aimed to assess incidence and determinants of SAMM in The Netherlands.[35] During this two-year period, women with SAMM were reported from all hospitals with a maternity unit. SAMM encompassed women with ICU admission, eclampsia or HELLP syndrome complicated by liver haemorrhage, uterine rupture, major obstetric haemorrhage (transfused with ≥4 units of blood) and other serious complications according to the local clinician. The results of the study were of invaluable importance, revealing rates of adverse maternal outcomes, options for prevention and improved management, and specific populations at risk such as women with a migration background.[35] The results contributed to improved clinical management, with emphasis given to the

management of hypertensive disorders, improved registration of risk categories and support of local audit.

Following the LEMMoN study, the importance of systematic, continued nationwide obstetric surveillance became clear. In 2013, a follow-up national obstetric surveillance system was set up, the NethOSS. The first set of outcomes consisted of eclampsia, cardiac arrest in pregnancy and amniotic fluid embolism.[36, 37] A decline in the incidence of eclampsia following the LEMMoN-period was demonstrated and thought to result from prompter management of hypertensive disorders following updated national guidelines. NethOSS contributed to new recommendations for clinical practice in relation to eclampsia, cardiac arrest, amniotic fluid embolism and management of COVID-19. [36,37,41,46]

Internationally, there are several other countries conducting national or multi-regional obstetric surveillance studies, with an aim to improve the quality of maternity care. Amongst others, UKOSS in the UK, B.OSS in Belgium, ItOSS in Italy, SOSS in Slovakia and NOSS in Denmark, Finland, Iceland, Norway and Sweden. The International Network of Obstetric Survey System (INOSS) is a collaborative platform of national and multi-regional obstetric survey systems.[38] INOSS aims to increase the knowledge of uncommon obstetric diseases and allows for comparisons of incidence, management and outcomes of therapeutic interventions between countries. Differences between countries may contribute to identification of improved management strategies. By pooling data from national surveillance systems, more robust conclusions can be drawn about pathophysiology and outcomes of rare pregnancy-related illness. Harmonization and use of common definitions is necessary.[47] Prior to this thesis, INOSS had conducted studies on eclampsia, uterine rupture and amniotic fluid embolism.[39-41] The next step should now be further research into peripartum hysterectomy and massive obstetric haemmorhage.

Peripartum hysterectomy

Following birth, surgical intervention by means of laparotomy is sometimes performed for severe unforeseen complications. It is a critical intervention that may be required in the management of women with life-threatening events. Incidence is usually low and mostly done to perform additional interventions or re-laparotomy after caesarean section. Interventions performed during (re-)laparotomy are directed to resolve haemorrhagic or septic complications. Women undergoing laparotomy, irrespective of mode of birth, will be at high risk for short- of long-term complications, including MNM and maternal death. Although laparotomy itself is not included in the MNM criteria as proposed by WHO, women who undergo laparotomy will have severe bleeding or infectious complications or undergo major surgery such as peripartum hysterectomy and could therefore be regarded as MNM. Women who underwent (re-)laparotomy certainly belong to the red MNM circle of maternal outcomes.(Figure 2)

Peripartum hysterectomy refers to removal of the uterus during pregnancy or shortly after birth. Different terms are used in the literature such as emergency peripartum hysterectomy, post-partum hysterectomy, obstetric hysterectomy or pregnancy-related hysterectomy. Most frequently, this procedure is performed for uncontrollable bleeding complications from atony, abnormally invasive placenta, but it is sometimes also done to manage uterine rupture, sepsis and first-trimester complications such as caesarean scar pregnancies. Therefore, these hysterectomies are an outcome of interest in studies of adverse maternal outcome in general and management of major obstetric haemorrhage in particular. Incidence was previously shown to differ between poorer (low- and lower middle-income) and richer settings (upper middle- and high-income): 28 vs. 7 per 10,000 births.[42] It may be considered as the most invasive surgical procedure in obstetrics, can be surgically challenging and is usually performed in emergency settings. At the same time, it is non-reversible in terms of permanently disabling fertility.

Management of massive postpartum haemorrhage requires acute intervention. Main pillars in clinical management are controlling the bleeding, haemodynamic blood and volume replacement, and correction of secondary coagulopathy. First interventions are usually performed in the labour room. These consist of uterine massage, administration of uterotonics and crystalloid fluids. When haemorrhage persists or is very severe, scaling up to mechanical and/or surgical intervention in the operating room is the next step. Depending on the mechanism or underlying cause of bleeding, interventions such as manual removal of the placenta, intrauterine balloon tamponade or restoring tissue damage are considered. A multidisciplinary approach with skilled anaesthesiologic support and prompt access to transfusion products as well as an intensive care unit is essential in such a life-threatening complication. Further management will consist of surgical intervention, which may require laparotomy following vaginal birth or additional interventions during caesarean section. Alternatively, radiological interventions like temporary iliac artery balloon occlusion or selective embolization of the uterine blood supply have made their entrance in obstetrics.

The plethora of possible interventions, lack of robust data and differences in management of massive obstetric haemorrhage between doctors and countries render it difficult to stipulate the optimal sequence or hierarchical order. Attempts have been made to compare the efficacy of different interventions, e.g. balloon tamponade vs. radiological embolization or balloon tamponade vs. uterine compression sutures. However, meta-analyses are hampered by wide variations in study design and randomised controlled trials are methodologically difficult given the low frequency and the acute setting in which interventions take place.[43]

Last resort intervention to stop uterine bleeding is inevitably hysterectomy itself. Due to its nature and association with postoperative complications, this procedure is sometimes seen as an adverse outcome in itself. Any delay, posing women at even higher risk due to severe hypovolaemia and coagulopathy, may

contribute to poor surgical outcome. On the other hand, removing the uterus in too early a stage in absence of alternative management options also exposes women to unnecessary risks. Can we define an optimal moment, in the cascade of blood loss, where extra delay in attempts of potentially unsuccessful interventions will be worse than resorting to hysterectomy? How far are clinicians inclined to go in order to preserve the womb? And is there any correlation with access to alternatives?

A major risk factor for hysterectomy is birth in the setting of one or more previous caesarean sections.[44] A scarred uterus is the main risk factor for an abnormally invasive placenta, which in turn, either diagnosed antenatally or not, leads to a very high risk of hysterectomy as was seen earlier in the case of *Mrs H*. If known antenatally, birth by caesarean section with planned caesarean hysterectomy is often the preferred management option, although conservative management or limited surgery are also practiced.[45] Many questions remain. How will the ever rising rates of caesarean sections impact on the national rates of hysterectomy? Will knowledge gaps related to the management of massive obstetric haemorrhage lead to differences in management between countries?

With trends of maternal mortality ratios showing remarkable differences, even between high-income countries, it is now time to provide an update of the MMR and causes of death in The Netherlands, and present the latest work of the AMSM. In light of the global caesarean section pandemic, The Netherlands is not an exception, although caesarean sections are increasing at a slower pace than in other parts of the world. We nevertheless hypothesise that the steady increase will have an impact on maternal outcomes and, as such, will take a closer look into causes of death following caesarean section, and compare the MMR following caesarean section to that of vaginal birth.

It must be noted, however, that maternal death is only the inner circle of morbidity, and zooming out, as we do in this thesis, is important to obtain a more complete view on maternal morbidity. With obstetric interventions so readily available, which is of course an important asset, there is a risk of these interventions being overused. Combined with increases in risk factors for adverse maternal outcomes in the general population, it is possible that larger numbers of women will experience severe adverse pregnancy outcomes. Both postpartum laparotomy and peripartum hysterectomy, mostly for bleeding complications, are likely to continue to be performed as management options for women with severe morbidity. The lack of international guidelines with regard to the management of life threatening obstetric haemorrhage might translate in differences in prevalence, indications and outcomes of peripartum hysterectomy. Platforms such as INOSS enable more robust analyses of such infrequent interventions on national and international scale, as we aim to show in this thesis.

OUTLINE OF THIS THESIS

First, the most recent MMR and causes of maternal mortality in The Netherlands for the years 2006-2018 are described in **Chapter 2**. A comparison is made with the previous studies of maternal mortality in the Netherlands. Lessons learned from the national confidential enquiry are presented.

Chapter 3 then zooms in on the association between maternal mortality in The Netherlands and mode of birth. The extent to which surgery was associated with maternal death, was evaluated by means of confidential enquiry into all deaths reported between 2006 and 2013. In addition, causes of death following caesarean section are presented and compared to previous studies in the Netherlands.

The second part of this thesis explores issues pertaining to maternal morbidity. Hysterectomy, laparotomy or re-laparotomy after birth are rare but potentially life-saving surgical procedures in obstetrics. In **Chapter 4**, a secondary analysis of the nationwide LEMMoN cohort, we identified national incidence rates for postpartum laparotomy related to SAMM in the Netherlands. Building on the previous chapter, hypothesis was that risk of postpartum laparotomy differed by mode of birth.

Focus then shifts to peripartum hysterectomy worldwide and in Europe. In **Chapter 5,** we present an update on prevalence, indications and outcomes of peripartum hysterectomy worldwide. In this literature review and meta-analysis, prevalence is compared between low-, middle- and high-income countries. Indications and outcomes are pooled to give estimates and insight into associated factors around the world.

Subsequently, we narrow down this exploration of peripartum hysterectomy to nine European countries. **Chapter 6** describes differences in prevalence between these member states of the International Network of Obstetric Survey Systems (INOSS). Data were pooled, and correlations between rates of peripartum hysterectomy and national (previous) caesarean section rates analysed. **Chapter 7** is a continuation of the same INOSS hysterectomy project, describing differences in management interventions, and maternal and neonatal outcomes in women who underwent peripartum hysterectomy. Given the lack of guidance in the literature on management of severe obstetric haemorrhage, we postulated that big differences would be observed in the management of postpartum haemorrhage leading up to hysterectomy.

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